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Clinical Characteristics, Diagnostic Findings and Therapeutic Outcome of Children Suffering Henoch-Schonlein Purpura: A Survey of Iranian Children

Mahtab Rahbar[1*], Rozita Hoseini[2], Shirin Behdmehr[3]

[1] Department of Pathology, Iran University of Medical Sciences, Tehran, Iran.
[2]Department of Pediatric Nephrology, Iran University of Medical Sciences, Tehran, Iran.
[3] Department of Pediatrics, Ali-Asghar Children's Hospital, Iran University of Medical Sciences, Tehran, Iran.

***Corresponding Author**
Dr. Mahtab Rahbar,
Email:rahbarrahbar@gmail.com

Abstract:

Background and Aim: Despite the spread of Henoch-Schonlein purpura (HSP) in all societies, especially in Asian children, no comprehensive study on HSP has been conducted in Iranian children and most of these reports are limited to disease cases or exclusively to patients with HSP. Therefore, this study was conducted to describe the clinical, diagnostic, and therapeutic approaches in children with HSP in Iran.

Methods: This historical cohort study was performed in all children suffering from HSPN hospitalized at Ali-Asghar Children's Hospital, Tehran between April 2006 and March 2017. The patients' baseline characteristics including demographics, clinical symptoms and laboratory parameters were all collected from hospital files. The patients were followed up for at least six months of initiating treatment and also for 12 to 120 months after treatment.

Results: Of 100 patients with HSP, 18 (11 boys and 7 girls) had indications for biopsy that were included in the study. The mean age of the participants was 7.72 ± 2.69 years. Nephrotic syndrome was found in 44.4% and nephritic syndrome in 61.1% of the patients. Hematuria was found in 66.7%, proteinuria in 66.7%, and hypertension in 38.9% of the patients. The mean serum creatinine was 1.0 ± 0.6 mg/dl with a mean GFR of 95 ± 5ml/min. Regarding pathological classification, 33.3% had class II and 66.7% had class III. With respect to therapeutic regimen, 61.1% were treated only with steroids while others were treated with a combination of steroids and immunosuppressant drugs. During the follow-up time, all patients were treated successfully with the mentioned regimens. In all treated subjects, proteinuria disappeared in all urine samples. Due to complete improvement in all patients, repeated renal biopsy was not indicated.

Conclusion: Kidney involvement occurs as nephritic syndrome in about two thirds of patients and as nephrotic syndrome in the remaining cases. In the majority of patients, treatment with steroids alone is successful although combined therapy with immunosuppressant drugs is required in the remaining patients. In summary, the therapeutic protocols are associated with a significant long-term recovery (a five-year recovery of 87.5% in our study).

Keywords: Henoch-Schonlein purpura; Nephritis; Nephrotic syndrome; Child.

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Introduction

Henoch-Schonlein purpura (HSP) was described by Heberdon about two hundred years ago when he treated two boys with purpuric rash, arthralgia and abdominal pain. Since then, thousands of articles have been published on HSP (1).

The incidence of this disease ranges between 6

and 24 per 100,000 children under the age of 17 years depending on the racial background (1). According to reports from Asian populations, the incidence of the disease is about 70 per 100,000 children annually (1).

Cutaneous purpura appears typically on the legs and hips, but may also appear on the arms, face or trunk (2).

About half of the children develop nephritis about 4 to 6 weeks after the onset of clinical manifestations (3). Most children with HSP nephritis called HSPN experience a mild form of the disease that manifests only with low-grade hematuria or proteinuria and has a high chance of healing; however, a small percentage of patients also exhibit nephrotic syndrome or renal dysfunction (3).

Therefore, it is very important to study the mechanism of the disease, its clinical manifestations, and effective treatments. The prognosis of the disease is favorable in children, but it may be associated with some serious complications, such as kidney involvement in the form of nephritis (4).

In many affected children, the outcome of the disease is favorable and the symptoms of the disease improve over the course of several days and eventually several months (5). The long-term morbidity of the disease depends on the degree of kidney involvement. In reports, the overall incidence of nephritic involvement occurring within 4 to 6 weeks after the onset of symptoms is about 30-50%, which is manifested with hematuria and proteinuria that are fortunately self-limited in many cases (6,7).

Nevertheless, about 20% of the children with HSPN (or 7% of all children with HSP) are likely to develop nephritis and/or nephrotic syndrome (8). In specialized centers, the proportion of children with HSPN progressing to renal failure or end-stage renal disease is reported to be about 1% to 7% (9).

Although there is no theoretical agreement on the treatment of patients with HSPN, patients with mild renal symptoms such as micro-hematuria, mild proteinuria, or normal renal function should be monitored for underlying kidney changes by histopathological assessments to select an appropriate treatment approach.

Despite the spread of HSPN in all societies, especially in Asian children, no comprehensive study of HSPN has been conducted in Iranian children and most of these reports are limited to disease cases or exclusively to patients with HSP. Therefore, this study was performed to describe the clinical, diagnostic, and therapeutic approaches in children with HSPN in Iran.

Methods

This historical cohort study was performed in all children suffering from HSPN that were hospitalized at Ali-Asghar Children's Hospital, Tehran between April 2006 and March 2017. The patients were diagnosed and included in the study based on the following diagnostic criteria for HSPN: presence of purpura, bowel angina, gastrointestinal bleeding, hematuria, age less than 20 years at the disease onset, and no evidence of other medical problems or any medication. The children with at least three of the above criteria were included in the present study.

The data were retrospectively collected from hospital files. The patients' baseline characteristics including demographics, clinical symptoms, type and location of involvement, macroscopic and microscopic signs such as hematuria and proteinuria, oliguria, edema, hypertension, and laboratory parameters including the serum levels of creatinine, total protein, albumin, triglyceride, and cholesterol were collected and entered into a checklist. Hypertension was defined as mean systolic or diastolic blood pressures higher than 95th percentile based on the body weight, height, and gender. The creatinine clearance was calculated based on the Schwartz Equation and low creatinine clearance was defined as GFR<60L/min. Nephritis was defined as the presence of gross or microscopic hematuria with and without proteinuria. Hematuria was also defined as positive dipstick results for hemoglobin or the presence of more than five RBCs per high-power field (HPF) in centrifuged urine samples. Proteinuria was defined as a urine dipstick positive for protein or presence of proteinuria higher than 5 mg/kg in 24-hour urine collection.

The patients with HSN were classified based on their clinical manifestations and according to the Meadow classification to grade I (microscopic hematuria), up to grade V (nephrotic-nephritic syndrome). The patients were also categorized

into the two groups including patients with grades I or II and a subgroup with grades III to V. All patients were assessed clinically and subclinically every two months. The indications for biopsy were continuous proteinuria, continuous hematuria, and nephritic or nephrotic syndrome with and without evidence of renal failure.

The indications for renal biopsy were also recorded. All samples with at least ten glomeruli were assessed with a microscope or immuno-florescence and the result was classified as grade I (minimal glomerular abnormalities); grade II (mesangial proliferation without crescents or sclerosing lesions); grade III (focal or diffuse segmental mesangial proliferation with < 50% crescents or sclerosing); grade IV (mesangial proliferation with 50% - 70% crescents or sclerosing lesions); grade V (>75% crescents or sclerosing); and grade VI (membranoproliferative-like lesions). Immunohistochemistry study was also considered using the serum containing fluorescent antibodies against C1q, C3, IgA, IgM, IgG, and fibrinogen. Regarding the pattern of the disorder, HSN was divided into three subgroups including group I (treated with anti-coagulative medication such as acetyl salicylic acid or diprydamol), group II (treated with glucocorticoids (oral prednisolone or pulse methylprednisolone), or group III (other immunosuppressive drugs such as cyclophosphamide or cyclosporine).

The clinical results were also classified according to Meadow criteria as group A (normal without evidence of hypertension, urinary tract anomalies, or proteinuria with normal serum creatinine), group B (minor urinary abnormalities such as mild proteinuria with and without hematuria), group C (active renal insufficiency with gross proteinuria and raised serum creatinine), and group D (renal failure with GFR less than 20L/min and raised serum creatinine). The patients were followed up for at least six months of initiating treatment (short-term follow-up) as well as for 12 to 120 months after treatment (long-term follow-up). Complete treatment was defined as grade A (absence of hypertension, urinary problems, proteinuria with normal serum creatinine) and other grades were considered as no response to treatment.

The results are presented as mean ± standard deviation (SD) for quantitative variables and as absolute frequency and percentage for categorical variables. Data normality was analyzed using the Kolmogorov-Smirnoff test. Categorical variables were compared using chi-square test or Fisher's exact test when more than 20% of cells with an expected count of less than 5 were observed. Quantitative variables were also compared with t test, Mann U test, ANOVA test or Kruskal-Wallis H test. The SPSS software version 16.0 for windows (SPSS Inc., Chicago, IL) was used for the statistical analysis. P values of 0.05 or less were considered statistically significant.

Results

In total, of 100 patients with HSPN, 18 (11 boys and 7 girls) had indications for biopsy that were included in the study (Table 1). The patients were followed up for 24 to 60 months with a mean time of 41 months. The mean age of the participants was 7.72 ± 2.69 years, ranging from 2 to 13 years with the peak of 6 years.

Table 1. Baseline characteristics of study population

Gender distribution	
Male	11 (61.1)
Female	7 (38.9)
Mean age (year)	7.72 ± 2.69
Renal manifestations	
Nephrotic syndrome	8 (44.4)
Nephritic syndrome	11 (61.1)
Hematuria	12 (66.7)
Proteinuria	12 (66.7)
Hypertension	7 (38.9)
Mean serum creatinine after treatment (mg/dl)	1.0 ± 0.6
Pathological classification	
Grade II	6 (33.3)
Grade III	12 (66.7)
Therapeutic protocol	
Steroid alone	11 (61.1)
Steroids, Cyclosporine, And azathioprine	3 (16.7)
Steroids, Cyclophosphamide	2 (11.1)
Steroids, Azathioprine	1 (6.5)
Steroids, Cyclosporine	1 (6.5)
Complete treatment response	18 (100)

No difference was observed in mean age between boys and girls (7.73 ± 3.06 years versus 7.71 ± 2.22 years, p = 0.992). Regarding renal involvement, nephrotic syndrome was found in 44.4%, and nephritic syndrome in 61.1%. Hematuria was found in 66.7%, proteinuria in 66.7%, and hypertension in 38.9% of the patients. The mean serum creatinine was 1.0 ± 0.6 mg/dl with a mean GFR of 95 ± 5ml/min. Regarding pathological classification, 33.3% had class II and 66.7% had class III. With respect to therapeutic regimen, 61.1% were treated only with steroids, 16.7% with a combination of steroids, cyclosporine, and azathioprine, 11.1% with steroids and cyclophosphamide, 5.6% with steroids and azathioprine, and 5.6% with steroids and cyclosporine.

Totally, in class II subgroup, 5 patients were treated with steroids and 1 with steroids and azathioprine, while in class III subgroup, 6 patients were treated with steroids alone, 3 with a combination of steroids, cyclosporine, and azathioprine, 2 with steroids and cyclophosphamide, and 1 with steroids and cyclosporine (Table 2). During the follow-up time, all patients were treated successfully using the above regimens. In all treated subjects, proteinuria disappeared in all urine samples. Due to complete improvement in all patients, repeated renal biopsy was not indicated.

Table 2. Treatment regimen according to pathological classification

Pathological class	Grade II	Grade III
Steroid alone	5	6
Steroids, Cyclosporine, And Azathioprine	0	3
Steroids, Cyclophosphamide	0	2
Steroids, Azathioprine	1	0
Steroids, Cyclosporine	0	1
Complete treatment response	0	0

Discussion

HSP is a rare disorder among children; however, there is wide disagreement on the treatment approach and the rate of response to treatment in these patients. In fact, due to the high distribution of nephrotic/nephritic syndrome in these patients, there is a need for complete treatment with combined corticosteroid treatments and immunosuppressive agents. However, long-term response to treatment remains questionable. On the other hand, information on the impact of genetic and racial factors on both the manifestations and extent of disease progression and on the response to treatment is vague.

In our society, there is so far no comprehensive information on the prevalence or clinical features of patients with HSPN. Therefore, the purpose of this study was to evaluate the clinical, diagnostic and therapeutic characteristics of these patients in the Iranian society. The results showed that the overall prevalence of HSP in the male gender was twice as high as in female gender. Second, the age range of HSPN was 6-9 years old, and mostly around 6 years. Renal involvement was found in about two thirds of patients in the form of nephritic syndrome and in the remaining as nephrotic syndrome.

A remarkable point was in the treatment approach of patients, so that two thirds of patients were treated with steroid therapy alone with favorable treatment outcomes and the rest of the patients needed combination therapy with steroids and immunosuppressive agents. It should be noted that tolerability levels for combination therapy have been reported to be low in some cases. Totally, the patients experienced an optimal long-term response (response to treatment was 87.5% within five years after treatment) and thus treatment with steroids with or without immunosuppressant drugs may be associated with a significant response in patients. Unfortunately, because of the limited number of patients, it was possible to evaluate the effective and predictive factors associated with the response to treatment. However, this is the first study in the Iranian society and therefore it provides Iranian specialists with valuable information about the management of these patients.

The results of previous reports presented by other communities are more or less consistent with the results of this study.

In a study by Feng et al (10), the peak age at HSP presentation ranged between 6 and 11 years, which was almost consistent with our study.

Moreover, all patients with nephrotic proteinuria experienced complete recovery and none of them developed end-stage renal disease. In a study by Delbet et al (11), 47% of the patients were treated with steroids alone, 37% were treated with pulsed methylprednisolone with steroids, and 18% did not receive steroids. During the follow-up, a recovery rate of 85% was achieved. Mizerska et al (12) found that proteinuria improved in 78% of the patients with mild HSPN and 87% of the patients with severe HSPN during a long-term follow up. Also, healing changes on histology were confirmed in 59% of patients.

In a study by Naija et al (13), the mean age of the patients was 7 years and the male to female ratio was 0.6, which was consistent with our study.

Microscopic hematuria was observed in 23.5%, proteinuria with and without hematuria in 20.5%, and nephrotic syndrome in 23.5%. The recovery rate was 76.4% in a 2-year follow-up, which was slightly less than the improvement rate in our study. Pirojsakul et al (14) reported that 65% of patients were free of proteinuria in six months. However, 35% of the patients had relapses on the last visit.

No recurrence was observed during the long-term follow-up in our study. Based on the clinical evidence, it appears that the factors associated with healing in patients with HSPN include the type of treatment protocol, the tolerance rate of this protocol, and the type and severity of the underlying kidney manifestation in such patients. However, accurate assessment of these factors requires studies with large sample sizes and long-term follow-ups.

Conclusion

In conclusion, it can be stated that nephritic involvement in children with HSP is twice more common in boys than in girls and the age of involvement is between 6 and 9 years old. Kidney involvement occurs as nephritic syndrome in about two thirds of patients and as nephrotic syndrome in the remaining cases. In the majority of patients (61.1%), treatment with steroids alone is effective; however, combined therapy with immunosuppressant drugs is required in the remaining patients. In summary, the therapeutic protocols are associated with a significant long-term recovery (a five-year recovery rate of 87.5% in our study).

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Conflict of Interest

Authors declared no conflict of interest.

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